A Stochastic Model of Oscillating Testosterone Levels in Men

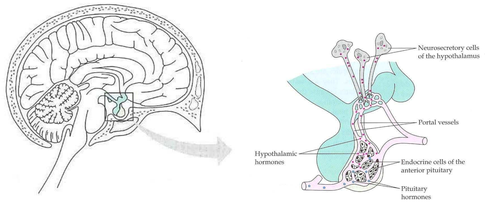
William J. Heuett (University of Colorado, Boulder) and Hong Qian (University of Washington, Seattle)

Abstract

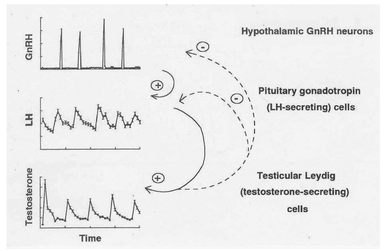
It has been observed that blood testosterone levels in men oscillate with a period of 2 to 3 hours. One simple, deterministic model of a negative feedback loop was proposed to describe this phenomenon, but it was recently proved that the model has a globally stable fixed point. Therefore, the deterministic model cannot observe oscillations. We take a closer look at this model from a different physical basis in which intrinsic fluctuations are considered. It turns out that sustained oscillations do arise in the continuous-time, discrete-state stochastic model. This demonstrates how oscillations can occur due to a switching behavior dependent on the random degradation of testoterone molecules in the system.

Introduction

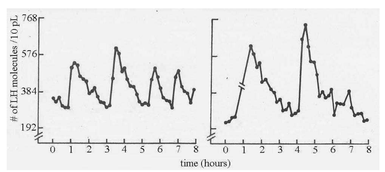
- Approximately 90% to 95% of testosterone in men is produced by the testes with typical blood testosterone levels in the range of 3 to 10 ng/mL.
- These levels have been experimentally observed to oscillate with a period of about 2 to 3 hours.
- An imbalance in testosterone levels can cause dramatic changes (mood, acne, and weight).
- Parts of the testosterone regulation pathway are associated with many other important processes in the body such as regulation of growth hormones and endorphins.
- Pharmaceutical interests in chemical castration (Goserelin, Lupron, and Depo-provera) and the creation of a male *pill*.



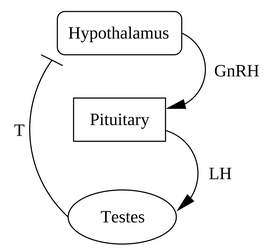
Cartoon of the hypothalamus and pituitary gland. Modified from Campbell (1996).



Plots of experimental data modified from Yen *et al.* (1999).



Plots of *LH* experimental data modified from Naftolin *et al.* (1973).



The Hormone Secretion Signaling System.

$GnRH =$ Gonadotropin Releasing Hormone

$LH =$ Luteinizing Hormone

$T =$ Testosterone

The Model

Let $R(t)$= # of *GnRH*, $L(t)$= # of *LH*, and $T(t)$= # of T molecules in the system at time t. Then we propose modeling this system such that

$$\frac{dR}{dt} = f(T) - b_1 R$$
$$\frac{dL}{dt} = g_1 R - b_2 L$$
$$\frac{dT}{dt} = g_2 L - b_3 T$$

where

$$f(T) = \frac{A}{K+T}.$$

- Goodwin (1964) first proposed this model in a deterministic form to demonstrate oscillatory behavior in enzymatic control processes.
- Smith (1980) studied a slight variation of the deterministic model involving a Hill coefficient in $f(T)$, and found that oscillations only exist for a physically unrealistic Hill coefficient of 8 or more.
- Murray (1989) suggested changing the deterministic model to include a time-delay in the production rate of T.
- Enciso and Sontag (2004) proved that the deterministic model has a globally stable fixed point (regardless of the length of the time-delay) and therefore does not have a limit cycle or sustained oscillations.

The fact that the deterministic form of this model does not capture the interesting behavior of the system under investigation does not mean that this model is useless. Rather, we find that the interesting behavior can be captured simply by reconsidering this model from a different physical basis. We do this by taking seriously the fact that events, such as production and degradation of hormone molecules, occur in an essentially random manner. As a result, we find that intrinsic fluctuations play a major role when there are low numbers of molecules present: an important factor since the hormones are typically present in low concentrations.

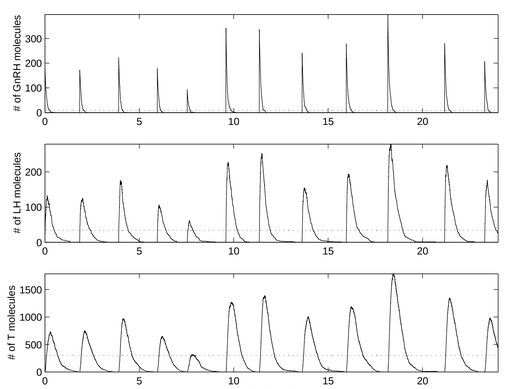
To incorporate intrinsic fluctuations, we approach the problem as a continuous-time, discrete-state Markov process where we are interested in the time-evolution of the chemical master equation

$$\frac{dP(\mathbf{n},t)}{dt} = \sum_{\mu=1}^{6} a_\mu(\mathbf{n}-\mathbf{s}_\mu)P(\mathbf{n}-\mathbf{s}_\mu,t) - a_\mu(\mathbf{n})P(\mathbf{n},t).$$

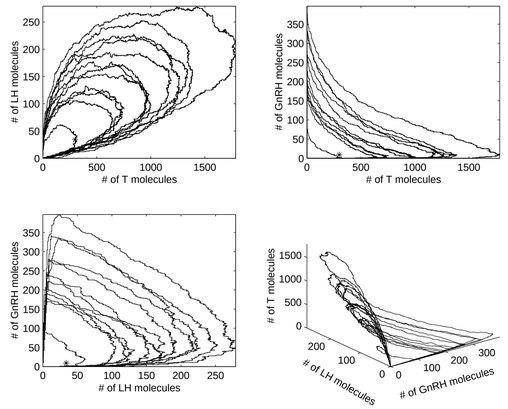
In this equation, the vector $\mathbf{n}$ has entries n_i that represent the number of molecules of species X_i in a well-mixed volume, $a_\mu(\mathbf{n})dt$ is the probability that reaction μ will occur in $(t, t+dt)$ given that the system is in state $\mathbf{n}$ at time t, and $\mathbf{s}_\mu$ is a stoichiometric vector defining the result of reaction μ. An exact simulation of the time-evolution of the chemical master equation is provided by the Gillespie algorithm. This method takes steps in time of length τ by choosing two random numbers, r_1 and r_2, from the unit uniform distribution and calculating the τ and μ for which

$$\tau = \frac{1}{a_0}\ln\left(\frac{1}{r_1}\right)$$
$$\sum_{k=1}^{\mu-1}\frac{a_k}{a_0} < r_2 \leq \sum_{k=1}^{\mu}\frac{a_k}{a_0}.$$

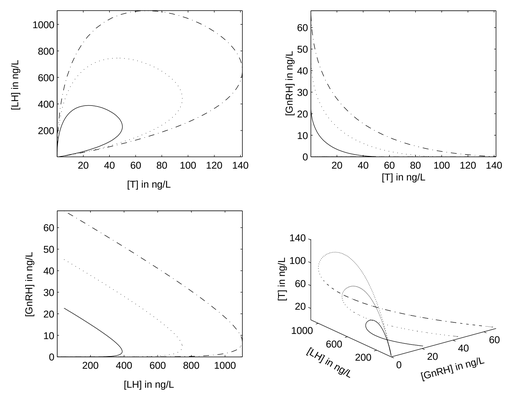
Results



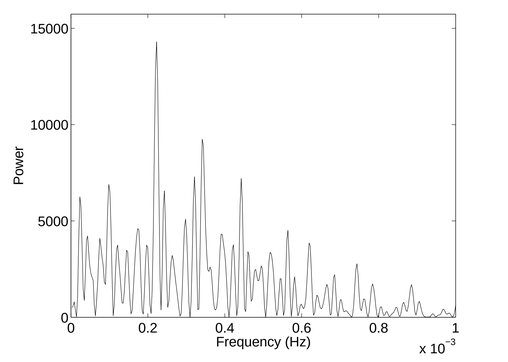
Simulation of hormone secretion for parameter values, $A = 10^{-4}$, $K = 10^{-7}$, $b_1 = 0.23$, $b_2 = 0.07$, $b_3 = 0.1$, $g_1 = 0.2618$, and $g_2 = 0.9015$. Average number of molecules are represented by dashed lines; average R is 9.09, average L is 33.92, and average T is 300.07. Volume is 10pL.



Two dimensional projections and three dimensional plot of simulation trajectory for the physical parameter values, $A = 10^{-4}$, $K = 10^{-7}$, $b_1 = 0.23$, $b_2 = 0.07$, $b_3 = 0.1$, $g_1 = 0.2618$, and $g_2 = 0.9015$. Average number of molecules are represented by asterisks.



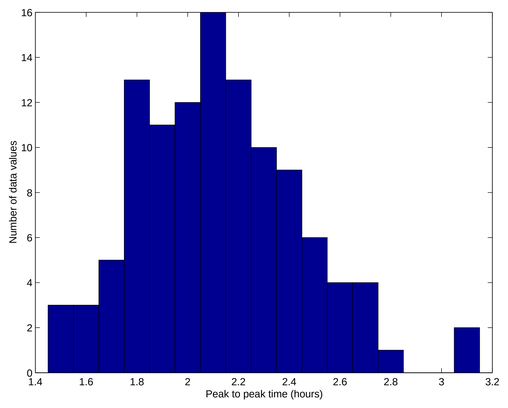
Two dimensional projections and three dimensional plot of the deterministic hormone secretion model trajectories using converted parameter values equivalent to those used in the stochastic simulation.



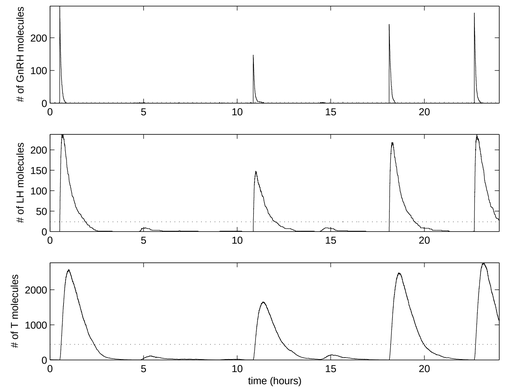
Lomb spectral analysis of data from the stochastic simulation. The largest peak corresponds to a frequency of 2.3429×10^{-4} Hz, which corresponds to a period of 1.2 hours.

Acknowledgments

The work of W.J.H. was supported, while a graduate student, by an NSF VIGRE fellowship and a DoD NDSEG fellowship. H.Q. was supported by NIH Grant Nos. GM068610 and HL072011. We thank James Burke, Daniel Beard, and Mark Kot for their helpful discussions and input. We also thank S.S.C. Yen and F. Naftolin for allowing us to use the figures from their work.



Peak-to-peak histogram of time intervals for the hormone secretion pathway over a 10 day time period.



Simulation to illustrate the the switching behavior. Parameter values are $A = 10^{-1}$, $K = 10^{-4}$, $b_1 = 0.23$, $b_2 = 0.032$, $b_3 = 0.046$, $g_1 = 0.2618$, and $g_2 = 0.9015$.

Conclusions

- By approaching the hormone model from a different physical basis we see how intrinsic fluctuations can incite oscillations for low numbers of molecules by way of a switching behavior.
- Even though the deterministic model has a globally stable fixed point, the stochastic model was able to capture the pulsatile behavior of the blood hormone levels.
- This approach provides a more realistic representation of the system than its deterministic, mass-action counterpart.
- This simple negative feedback model can be applied to study several different biological systems.

REFERENCES

Campbell, N.A. (1996) *Biology*, 4th ed. The Benjamin/Cummings Publishing Company, Menlo Park, California.

Enciso, G. and Sontag, E.D. (2004) On the stability of a model of testosterone dynamics. *J. Math. Bio.* **49**, 627-634.

Gillespie, D.T. (1976) A General Method for Numerically Simulating the Stochastic Time Evolution of Coupled Chemical Reactions. *J. of Comp. Phys.* **22**, 403–434.

Gillespie, D.T. (1977) Exact stochastic simulation of coupled chemical reactions. *J. Phys. Chem.* **81**, 2340-2361.

Goodwin, B.C. (1965) Oscillatory behavior in enzymatic control processes. *Adv. Enz. Reg.* **3**, 425-438.

Murray, J.D. (2002) *Mathematical biology, I: an introduction*, 3rd ed. Springer, New York.

Naftolin, F., Judd, H.L., and Yen, S.S.C. (1973) Pulsatile patterns of gonadotropins and testosterone in man: The effects of clomiphene with and without testosterone. *J. Clin. Endocrinol. Metab.* **36**, 285-288.

Smith, W.R. (1980) Hypothalamic regulation of pituitary secretion of luteinizing hormone. II Feedback control of gonadotropin secretion. *Bull. Math. Bio.* **42**, 57-78.

Yen, S.S.C., Jaffe, R.B., and Barbieri, R.L. (1999) *Reproductive endocrinology: physiology, pathophysiology, and clinical management*, 4th ed. Saunders, Philadelphia.

This poster was prepared with Brian Wolven's Poster LaTeX macros v2.1.

Table 1:

Table 2:

Fig. 1.—